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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/478,668	01/06/00	BANNON G	HS-102-DIV

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EXAMINER	
HUYNH,P	
ART UNIT	PAPER NUMBER
1644	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/478,668	Applicant(s) BANNON ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Thee* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute; cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/6/00; 4/6/01* .

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. **Please note** the location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Dr. Phuong N. Huynh, Art Unit 1644, Group 1640, Technology Center 1600.

2. Claims 14-29 are pending.

3. Preliminary amendment filed 1/6/00 (Paper No. 9) is acknowledged.
Claims 1-14 have been canceled.

4. Applicant's election without traverse of Group I claim 1, claims 14-29, filed 10/4/00, is acknowledged.

5. Claims 14-29 are being acted upon in this Office Action.

6. The drawings, filed 1/6/00, are approved.

7. The specification is objected to because there is also a typographical error on page 15 line 20, "Ifn-ξ" should have been "IFNγ".

8. Claim 24 is objected to because "IL 12, IL 16, IL 18, Ifn-γ and immune stimulatory sequences". Applicants should amend the claim recite "IL-12, IL-16, IL-18, IFNγ" and the particular specific immune stimulatory sequence that is disclosed in the specification.

9. The filing date of the instant claims 14, 16-18, 22-24, is deemed to be the filing date of the priority application USSN 09/141,220, filed 08/27/98, as the previous priority applications provisional 60/073,283, 60/074,633, 60/074,624, 60/074,590 do not support the claimed limitations of "modified allergen activates T cells" and "binds IgG" in the instant application. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicants are reminded that such

priority for the instant limitations requires a written description and enablement under 35 U.S.C. § 112, first paragraph.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 14, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified allergen from peanut consisting of IgE binding epitopes from Ara h1, Ara h2 and Ara h3 (See page 26-27) wherein the IgE binding site (epitope) has at least one amino acid residues changes to alanine or methionine by amino acid substitution (See page 24, line16-18; page 28, line 6-9), the resulting modified allergen Ara h1 or Ara h2 binds less IgE than unmodified recombinant allergen, and only the modified allergen Ara h2 has been shown to bind similar amount of IgG and to stimulate T cell proliferation (page 28), does not reasonably provide enablement for (1) *any* other modified allergen "having at least one amino acid bound by a compound so that the site no longer binds IgE" as recited in claim 14, (2) *any* other modified allergen which is mutated by "substituting a hydrophobic amino acid in the center of one or more of the IgE binding sites with a neutral or hydrophilic amino acid" other than alanine and glycine, (3) *any* other modified allergen wherein the IgE binding is blocked by a compound reacted with at least one amino acid present in an IgE binding site, and (4) *any* other modified allergen wherein the binding of IgE is blocked by reaction of the allergen with an antibody which blocks IgE binding to one of or more IgE sites but still allows the allergen to still activate T cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the claim encompasses *any* modified allergen other than the peanut allergen consisting of IgE binding epitopes from Ara h1, Ara h2 and Ara h3 where the immunodominant IgE binding epitopes are mutated to non-IgE binding epitopes by a single amino acid substitution with *any* amino acid other than alanine and glycine.

The specification as filed discloses only modified allergen from peanut consisting of IgE binding epitopes from Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

The specification as filed does not disclose *any* critical IgE binding epitopes from legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes other than peanut Ara h1, Ara h2, Ara h3. The specification fails to provide guidance as to which amino acids within the IgE binding epitopes of *any* allergens other than Ara h1, Ara h2 and Ara h3 are critical for IgE binding. The specification also fails to provide guidance as to which amino acid within the IgE binding epitopes of *any* allergen other than peanut Ara h1, Ara h2 and Ara h3 can be change to alanine or methionine, in turn, would decrease IgE binding, maintain IgG binding and increase T cell proliferation. The specification also fails to provide guidance as to which type of amino acid within the IgE binding epitopes of any allergen other than peanut Ara h1, Ara h2 and Ara h3 can be change other than alanine or methionine, in turn, would decrease IgE binding, would maintain IgG binding and would increase T cell proliferation.

There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid

sequence can have dramatic effects on the protein's function. Fasler *et al.* (PTO 892) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 with either a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular). Burks *et al.* (PTO 1449) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Stanley et al (PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Colman *et al* teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular).

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. As such, further research would be required. In view of the quantity of experimentation necessary, the insufficient number

of working examples, the unpredictability of the art, the insufficient guidance and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 14, 19, 24 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "having at least one amino acid bound by a **compound**" as recited in claims 1 and 19 is indefinite and vague. As written, it is unclear what the "compound" is. One of ordinary skill in the art cannot apprise the metes and bounds of the claimed invention.

The phrase "immune stimulatory sequence" as recited in claim 24 is indefinite and vague. As written, it is not clear what sequence is considered immune stimulatory. It is suggested that applicants amend the claim to recite a specific sequence, see page 7, line5 of specification, for example.

The phrase "bird" as recited in claim 28 has no support in the specification as filed.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph because claims 24 recites a composition (allergen and adjuvant) while dependent claim 14 is a compound (modified allergen).

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 14-23, 25-27, 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449; see entire document).

Burks *et al* teach IgE binding epitopes of Ara h1 from peanut of the Legume family play an important role in the disease process. All the immunodominant Ara h1 peptides or portion of the peptide can be mutated to non-IgE binding epitopes by single amino acid changes (See Fig. 6-7, in particular). The modified allergen is mutated in the center of one or more IgE binding epitopes by substituting a hydrophobic amino acid (Ala) in the center of one or more of the IgE binding sites with a neutral (Gly) or hydrophilic (Ser) amino acid (See Fig 7, A25G, column 2, paragraph 1, in particular). The modified allergen is based on a protein obtained from legumes which peanut is part of the family. The modified allergen is made by the process of identifying one or more IgE binding sites in an allergen, mutating one or more amino acid in an IgE binding site, screening for IgE binding to the mutated allergen and selecting the modified allergens with the least binding to IgE (See Fig 2 and 3; page 247; page 246 for IgE-binding assay, in particular). The reference further teaches that there are at least 23 different IgE recognition sites on peanut allergen Ara 1 distributed throughout the protein and the modified allergen is a portion of a protein (See Figs 1-3, Fig 6, page 339, column 1, in particular). It is possible to mutate the Ara h1 allergen to a protein so that it no longer binds IgE and this could be used to replace its allergenic homologue in the peanut genome to develop a hypoallergenic peanut and for making and using hypogenic modified allergen for the purpose of diagnostic and immunotherapy (See page 339, column 1; page 245 column 2, second paragraph). Claims 14-15, 20-21 are included in this rejection because the functional properties (activates T cells and binds IgG) of the claimed modified allergen inherently has the same intrinsic structural properties as the reference modified allergen Ara h1. Claims 25-27 included in this rejection because the claims recite a product by process. The recitation of a process limitation in claim 25-27 is not seen as further limiting the claimed product, as it is presumed that equivalent products can be obtained by multiple routes. The burden is on the applicant to establish a patentable distinction between the claimed and referenced antibodies/methods. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). Thus, the reference teachings anticipate the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 14 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burks *et al* (Eur. J. Biochem. 245: 334-339; 1997, PTO 1449; see entire document) in view of Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996, PTO 892).

The teachings of Burks have been discussed supra.

The claimed invention in claim 24 differs by the recitation of modified allergen is formulated to include an adjuvant from the group consisting of IL-12, IL-16, IL-18, IFNγ and immune stimulatory sequences.

Hoyne *et al.* teach patients receiving the PLA-2 specific peptides from bee venom demonstrated a decrease in allergen specific IgE and a corresponding rise in IgG levels; most patients reported a significant improvement in clinical symptoms (See page 183, column 1, paragraph 2, in particular). Hoyne *et al.* further teach peptide-mediated regulation of allergic immune response and a successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production (See page 180, column 2, in particular). The reference further teaches that the key to successful immunotherapy may dependent on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ or immunizing with recombinant live vaccine

vectors such as mycobacteria expressing defined allergens or fragments (See page 183, column 2, paragraph 2, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made would have been motivated to formulate modified allergen in the presence of IL-12 or IFNγ because the key to a successful peptide-based immunotherapy depends on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ because IL-12 or IFNγ would down-regulate ongoing Th2 responses in vivo by suppressing IgE production as taught by Hoyne (See page 183, column 2, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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June 14, 2001

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